10588070

* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 16:32:57 ON 18 JAN 2009

=> file reg
COST IN U.S. DOLLARS   SINCE FILE   TOTAL
                                                         ENTRY   SESSION
FULL ESTIMATED COST   0.22   0.22

FILE 'REGISTRY' ENTERED AT 16:33:06 ON 18 JAN 2009
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 16 JAN 2009 HIGHEST RN 1094159-77-9
DICTIONARY FILE UPDATES: 16 JAN 2009 HIGHEST RN 1094159-77-9

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH July 5, 2008.

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

REGISTRY includes numerically searchable data for experimental and
predicted properties as well as tags indicating availability of
experimental property data in the original document. For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

=> s 33507-63-0/rn
L1   1 33507-63-0/RN

=> d l1

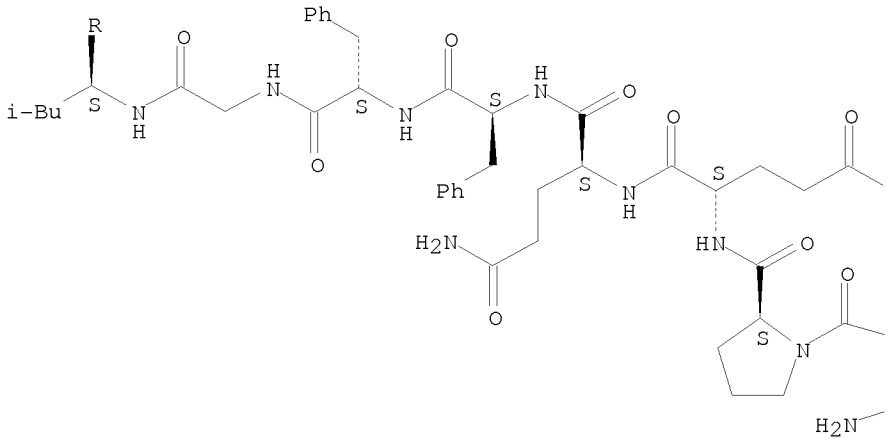
L1   ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN
RN   33507-63-0 REGISTRY
ED   Entered STN: 16 Nov 1984
CN   Substance P (CA INDEX NAME)
OTHER NAMES:
CN   1: PN: US20020037833 SEQID: 1 unclaimed sequence
CN   21: PN: WO0181408 SEQID: 44 claimed protein
CN   2: PN: JP2005049164 SEQID: 2 claimed protein
CN   36: PN: WO2007058336 SEQID: 36 claimed protein
CN   44: PN: WO2005016244 PAGE: 68 claimed protein
CN   690: PN: WO2004005342 PAGE: 46 claimed protein
CN   L-Methioninamide, L-arginyl-L-prolyl-L-lysyl-L-prolyl-L-glutaminyl-L-
     glutaminyl-L-phenylalanyl-L-phenylalanylglycyl-L-leucyl-
CN   Neurokinin P
CN   Substance P (1-11)
CN   Substance P (peptide)
CN   Substance P (smooth-muscle stimulant)
FS   PROTEIN SEQUENCE; STEREOSEARCH
DR   12769-48-1, 11035-08-8
MF   C63 H98 N18 O13 S
CI   COM

LC STN Files: ADISINSIGHT, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CASREACT, CHEMCATS, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL, USPATOLD
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

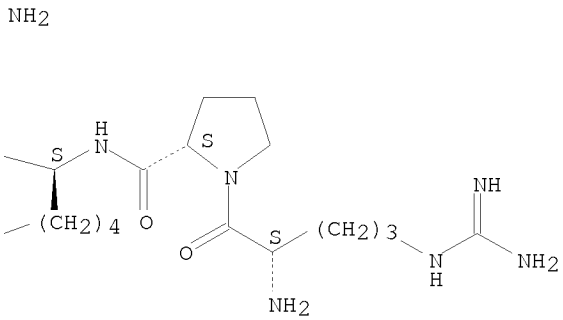
RELATED SEQUENCES AVAILABLE WITH SEQLINK

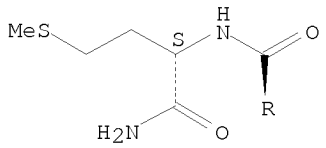
Absolute stereochemistry.

PAGE 1-A



PAGE 1-B





PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

15387 REFERENCES IN FILE CA (1907 TO DATE)
520 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
15411 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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=> s 147116-64-1p/rn
L3            0 147116-64-1P/RN

=> s 147116-64-1/rn
L4            1 147116-64-1/RN

=> d 14

L4   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2009 ACS on STN
RN   147116-64-1  REGISTRY
ED   Entered STN:  21 Apr 1993
CN   1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[[2-methoxy-5-(1-
     methylethyl)phenyl]methyl]-, (2S,3S)-  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[[2-methoxy-5-(1-
     methylethyl)phenyl]methyl]-, (2S-cis)-
OTHER NAMES:
CN   CJ 11974
CN   Ezlopitant
FS   STEREOSEARCH
MF   C31 H38 N2 O
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS, EMBASE,
       IMSRESEARCH, IPA, MEDLINE, PHAR, PROUSDDR, TOXCENTER, USAN, USPAT2,
       USPATFULL

Absolute stereochemistry.  Rotation (-).
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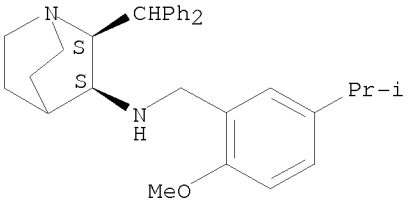


10588070

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

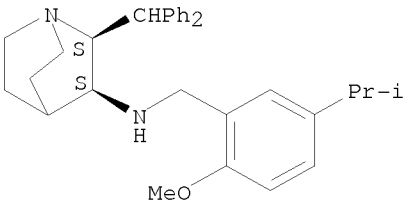
61 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
61 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s 147116-64-1/rn
L5 1 147116-64-1/RN

=> d l5

L5 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN
RN 147116-64-1 REGISTRY
ED Entered STN: 21 Apr 1993
CN 1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[[2-methoxy-5-(1-methylethyl)phenyl]methyl]-, (2S,3S)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[[2-methoxy-5-(1-methylethyl)phenyl]methyl]-, (2S-cis)-
OTHER NAMES:
CN CJ 11974
CN Ezlopitant
FS STEREOSEARCH
MF C31 H38 N2 O
CI COM
SR CA
LC STN Files: ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CA, CAPLUS, EMBASE, IMSRESEARCH, IPA, MEDLINE, PHAR, PROUSDDR, TOXCENTER, USAN, USPAT2, USPATFULL

Absolute stereochemistry. Rotation (-).



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

61 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
61 REFERENCES IN FILE CAPLUS (1907 TO DATE)

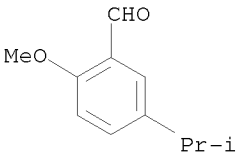
=> s 85902-68-7/rn
L6 1 85902-68-7/RN

=> d l6

L6 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN
RN 85902-68-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN Benzaldehyde, 2-methoxy-5-(1-methylethyl)- (CA INDEX NAME)

10588070

OTHER NAMES:
CN 2-Methoxy-5-isopropylbenzaldehyde
CN 5-Isopropyl-2-methoxybenzaldehyde
MF C11 H14 O2
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, CHEMCATS, CSCHEM,
      TOXCENTER, USPATFULL
        (*File contains numerically searchable property data)



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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              1 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             18 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s 147780-91-4/rn
L7   1 147780-91-4/RN

=> d l7

L7 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN
RN 147780-91-4 REGISTRY
ED Entered STN: 27 May 1993
CN 1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[[2-methoxy-5-(1-
    methylethyl)phenyl]methyl]-, (2S,3S)-, methanesulfonate (1:1) (CA INDEX
    NAME)
OTHER CA INDEX NAMES:
CN 1-Azabicyclo[2.2.2]octan-3-amine, (2S)-2-(diphenylmethyl)-N-[[2-methoxy-5-
    (1-methylethyl)phenyl]methyl]-, (3S)-, monomethanesulfonate (9CI)
CN 1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[[2-methoxy-5-(1-
    methylethyl)phenyl]methyl]-, (2S-cis)-, monomethanesulfonate
FS STEREOSEARCH
MF C31 H38 N2 O . C H4 O3 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

    CM 1

    CRN 147116-64-1
    CMF C31 H38 N2 O

Absolute stereochemistry. Rotation (-).

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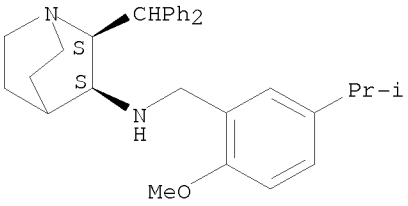
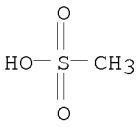


CM 2

CRN 75-75-2
CMF C H4 O3 S



4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s 147780-92-5/rn
L8 1 147780-92-5/RN

=> d l8

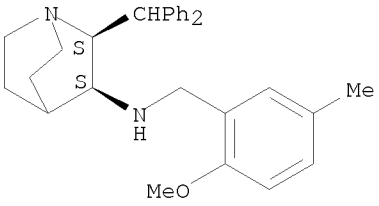
L8 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN
RN 147780-92-5 REGISTRY
ED Entered STN: 27 May 1993
CN 1-Azabicyclo[2.2.2]octan-3-amine, (2S)-2-(diphenylmethyl)-N-[(2-methoxy-5-methylphenyl)methyl]-, (3S)-, monomethanesulfonate (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[(2-methoxy-5-methylphenyl)methyl]-, (2S-cis)-, monomethanesulfonate
FS STEREOSEARCH
MF C29 H34 N2 O . C H4 O3 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

CRN 147116-66-3
CMF C29 H34 N2 O

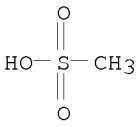
Absolute stereochemistry.

10588070



CM 2

CRN 75-75-2
CMF C H4 O3 S



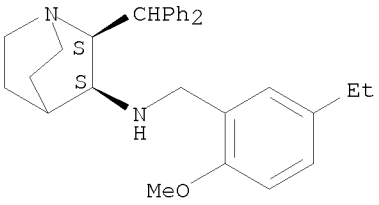
3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s 147116-65-2/rn
L9 1 147116-65-2/RN

=> d l9

L9 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN
RN 147116-65-2 REGISTRY
ED Entered STN: 21 Apr 1993
CN 1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[(5-ethyl-2-methoxyphenyl)methyl]-, (2S,3S)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[(5-ethyl-2-methoxyphenyl)methyl]-, (2S-cis)-
FS STEREOSEARCH
MF C30 H36 N2 O
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



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PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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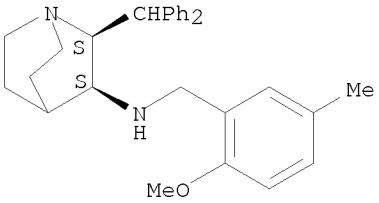
22 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s 147116-66-3/rn
L10 1 147116-66-3/RN

=> d l10

L10 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN
RN 147116-66-3 REGISTRY
ED Entered STN: 21 Apr 1993
CN 1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[(2-methoxy-5-methylphenyl)methyl]-, (2S,3S)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[(2-methoxy-5-methylphenyl)methyl]-, (2S-cis)-
FS STEREOSEARCH
MF C29 H34 N2 O
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

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18 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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=> d l11

L11 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN
RN 147780-93-6 REGISTRY
ED Entered STN: 27 May 1993
CN 1-Azabicyclo[2.2.2]octan-3-amine, (2S)-2-(diphenylmethyl)-N-[(5-ethyl-2-methoxyphenyl)methyl]-, (3S)-, monomethanesulfonate (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[(5-ethyl-2-methoxyphenyl)methyl]-, (2S-cis)-, monomethanesulfonate
FS STEREOSEARCH
MF C30 H36 N2 O . C H4 O3 S
SR CA

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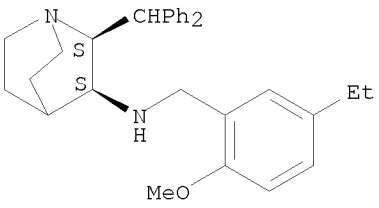
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

CRN 147116-65-2
CMF C30 H36 N2 O

Absolute stereochemistry.



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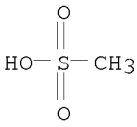

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3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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L12 1 147116-67-4/RN

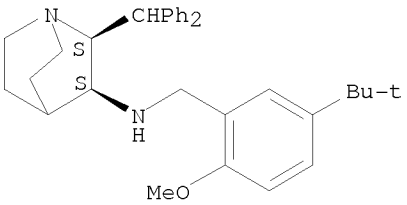
=> d l12

L12 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN
RN 147116-67-4 REGISTRY
ED Entered STN: 21 Apr 1993
CN 1-Azabicyclo[2.2.2]octan-3-amine, N-[[5-(1,1-dimethylethyl)-2-methoxyphenyl]methyl]-2-(diphenylmethyl)-, (2S,3S)- (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Azabicyclo[2.2.2]octan-3-amine, N-[[5-(1,1-dimethylethyl)-2-methoxyphenyl]methyl]-2-(diphenylmethyl)-, (2S-cis)-
OTHER NAMES:
CN (2S,3S)-2-Benzhydryl-N-(5-tert-butyl-2-methoxybenzyl)quinuclidin-3-amine
CN Maropitant
FS STEREOSEARCH
MF C32 H40 N2 O
CI COM
SR CA
LC STN Files: AGRICOLA, CA, CAPLUS, CASREACT, CIN, PATDPASPC, PROMT, PROUSDDR, TOXCENTER, USAN, USPATFULL

Jagoe

10588070

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

27 REFERENCES IN FILE CA (1907 TO DATE)
27 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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L13 1 147780-94-7/RN

=> d l13

L13 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN
RN 147780-94-7 REGISTRY
ED Entered STN: 27 May 1993
CN 1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[[2-methoxy-5-(1-methylpropyl)phenyl]methyl]-, methanesulfonate (1:1) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[[2-methoxy-5-(1-methylpropyl)phenyl]methyl]-, monomethanesulfonate (9CI)
MF C32 H40 N2 O . C H4 O3 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

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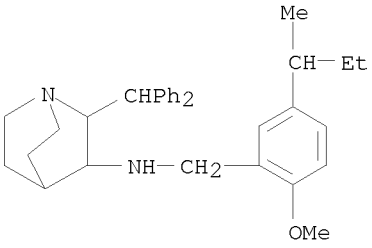
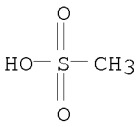
CMF C32 H40 N2 O



CM 2

CRN 75-75-2
CMF C H4 O3 S

10588070



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1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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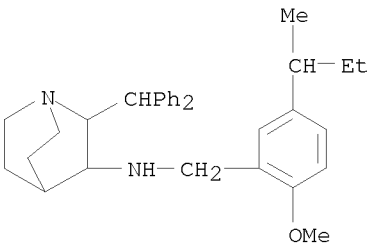
L14 1 147116-68-5/RN

=> d l14

L14 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2009 ACS on STN
RN 147116-68-5 REGISTRY
ED Entered STN: 21 Apr 1993
CN 1-Azabicyclo[2.2.2]octan-3-amine, 2-(diphenylmethyl)-N-[[2-methoxy-5-(1-methylpropyl)phenyl]methyl]- (CA INDEX NAME)
MF C32 H40 N2 O
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, USPATFULL



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

14 REFERENCES IN FILE CA (1907 TO DATE)
14 REFERENCES IN FILE CAPLUS (1907 TO DATE)

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(FILE 'HOME' ENTERED AT 16:32:57 ON 18 JAN 2009)

FILE 'REGISTRY' ENTERED AT 16:33:06 ON 18 JAN 2009
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L2 0 S 142035-23-2P/RN
L3 0 S 147116-64-1P/RN
L4 1 S 147116-64-1/RN
L5 1 S 147116-64-1/RN
L6 1 S 85902-68-7/RN
L7 1 S 147780-91-4/RN
L8 1 S 147780-92-5/RN
L9 1 S 147116-65-2/RN
L10 1 S 147116-66-3/RN

Jagoe

10588070

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L11           1 S 147780-93-6/RN
L12           1 S 147116-67-4/RN
L13           1 S 147780-94-7/RN
L14           1 S 147116-68-5/RN

=> file medicine
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      30.36      30.58

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FILE 'DDFU' ACCESS NOT AUTHORIZED

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FILE 'DRUGMONOG2' ENTERED AT 16:40:30 ON 18 JAN 2009
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FILE 'USPATOLD' ENTERED AT 16:40:30 ON 18 JAN 2009
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FILE 'USPAT2' ENTERED AT 16:40:30 ON 18 JAN 2009
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L3             0 S 147116-64-1P/RN
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L6             1 S 85902-68-7/RN
L7             1 S 147780-91-4/RN
L8             1 S 147780-92-5/RN
L9             1 S 147116-65-2/RN
L10            1 S 147116-66-3/RN
L11            1 S 147780-93-6/RN
L12            1 S 147116-67-4/RN
L13            1 S 147780-94-7/RN
L14            1 S 147116-68-5/RN

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L15        242 L4 OR L5 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14

=> s cyclodextrin or ?cyclodextrin or beta cyclodextrin or 2 hydroxypropyl beta cyclodextrin
or sulfobutyl ether beta cyclodextrin
LEFT TRUNCATION IGNORED FOR FILE 'ADISINSIGHT'
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L16     169524 CYCLODEXTRIN OR ?CYCLODEXTRIN OR BETA CYCLODEXTRIN OR 2 HYDROXYP
               ROPYL BETA CYCLODEXTRIN OR SULFOBUTYL ETHER BETA CYCLODEXTRIN
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would be searched as 'FLAVONOID.'

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Implied proximity is used in search fields indexed as single words,
for example, the Basic Index.

=> s l16 and l15
L17          8 L16 AND L15

=> s preservative or thimerosol or propylene glycol or phenol or meta cresol or m cresol or
m methylphenol or m methylphenylol or m hydroxytoluene or m oxytoluene or me toluol or 1
hydroxy 3 methylbenzene or 3 hydroxytoluene or 3 methylphenol or m cresylic acid or
metacresol or m Kresol
   6 FILES SEARCHED...
   8 FILES SEARCHED...
  15 FILES SEARCHED...
  26 FILES SEARCHED...
  32 FILES SEARCHED...
  33 FILES SEARCHED...
  34 FILES SEARCHED...
L18    1700833 PRESERVATIVE OR THIMEROSOL OR PROPYLENE GLYCOL OR PHENOL OR META
                CRESOL OR M CRESOL OR M METHYLPHENOL OR M METHYLPHENYLOL OR M
               HYDROXYTOLUENE OR M OXYTOLUENE OR ME TOLUOL OR 1 HYDROXY 3 METHY
               LBENZENE OR 3 HYDROXYTOLUENE OR 3 METHYLPHENOL OR M CRESYLIC
               ACID OR METACRESOL OR M KRESOL

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L19          6 L17 AND L18

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IMSPRODUCT, KOSMET, NUTRACEUT, PCTGEN, PHARMAML, USGENE'.
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L20 6 DUP REM L19 (0 DUPLICATES REMOVED)

=> d l20 1-6 ibib, kwic, ind

L20 ANSWER 1 OF 6 USPATFULL on STN
ACCESSION NUMBER: 2007:282883 USPATFULL
TITLE: Multiple mode display apparatus
INVENTOR(S): Oakley, Nicholas W., Portland, OR, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20070247432	A1	20071025
APPLICATION INFO.:	US 2006-588070	A1	20061024 (11)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-185154, filed on 27 Jun 2002, GRANTED, Pat. No. US 7126588
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BLAKELY, SOKOLOFF, TAYLOR & ZAFMAN LLP, Seventh Floor, 12400 Wilshire Boulevard, Los Angeles, CA, 90025-1026, US
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 16 Drawing Page(s)
LINE COUNT: 820
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ST antimicrobial preservative cyclodextrin liq dosage form
IT Tachykinin antagonists
(NK1 receptor antagonists; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT Preservatives
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT Drug delivery systems
(liqs.; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT Drug delivery systems
(parenterals; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT 35963-20-3 85943-26-6 155681-48-4
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT 147116-67-4P
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT 359875-09-5P 863879-46-3P
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT 54-64-8, Thimerosal 57-55-6, Propylene glycol, biological studies 108-39-4, m-Cresol, biological studies 108-95-2, Phenol, biological studies 7585-39-9, β -Cyclodextrin 7585-39-9D, β -Cyclodextrin, ethers 147116-68-5 863879-43-0 863879-44-1 863879-45-2
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
INCL INCLM: 345/169.000

10588070

NCL NCLM: 345/169.000
IC IPCI G09G0005-00 [I,A]
IPCR G09G0005-00 [I,C]; G09G0005-00 [I,A]; G06F0001-16 [I,C*];
G06F0001-16 [I,A]

CHEMICAL ABSTRACTS INDEXING COPYRIGHT 2009 ACS on STN

	PATENT	KIND	DATE
OS CA 143:272554 *	WO 2005082416	A2	20050909

* CA Indexing for this record included
CC 63-6 (Pharmaceuticals)
ST antimicrobial preservative cyclodextrin liq dosage form
IT Tachykinin antagonists
(NK1 receptor antagonists; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT Preservatives
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT Drug delivery systems
(liqs.; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT Drug delivery systems
(parenterals; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT 35963-20-3 85943-26-6 155681-48-4
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT 147116-67-4P
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT 359875-09-5P 863879-46-3P
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT 54-64-8, Thimerosal 57-55-6, Propylene glycol, biological studies 108-39-4, m-Cresol, biological studies 108-95-2, Phenol, biological studies 7585-39-9, β -Cyclodextrin 7585-39-9D, β -Cyclodextrin, ethers 147116-68-5 863879-43-0 863879-44-1 863879-45-2
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

L20 ANSWER 2 OF 6 USPATFULL on STN
ACCESSION NUMBER: 2007:177961 USPATFULL
TITLE: Nk-1 receptor antagonists anesthesia recovery
INVENTOR(S): Hickman, Mary Anne, East Lyme, CT, UNITED STATES
Miskell, Christine, Colchester, CT, UNITED STATES

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20070155782	A1	20070705	
APPLICATION INFO.:	US 2005-587590	A1	20050106	(10)
	WO 2005-IB10		20050106	
			20060728	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 2004-540697P	20040130 (60)

Jagoe

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PHARMACIA & UPJOHN, 7000 Portage Road, KZO-300-104, KALAMAZOO, MI, 49001, US
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1-10
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 528
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM Preferentially, the composition is administered parenterally, with the pharmaceutical composition further comprising a pharmaceutically acceptable cyclodextrin. Preferentially, the cyclodextrin is .beta.-cyclodextrin, hydroxypropyl .beta.-cyclodextrin, sulfobutylether .beta.-cyclodextrin or substituted cyclodextrins. In a preferred embodiment, the cyclodextrin is sulfobutylether .beta.-cyclodextrin and the NK-1 receptor antagonist is (2S,3S)-2-benzhydryl-N-(5-tert-butyl-2-methoxybenzyl)quinuclidin-3-amine.

SUMM In a preferred embodiment, the composition further comprises a pharmaceutically acceptable preservative, preferably, meta-cresol.

SUMM The term "cyclodextrin" as used herein means a cyclic oligosaccharide. Cyclodextrins typically vary in shape and size, but define a hydrophobic cavity and can form inclusion compounds with other organic molecules, with salts, and with halogens either in solid state or in aqueous solution. Methods for preparing cyclodextrins are well known to those of skill in the art and many cyclodextrins are commercially available. There are three main types of cyclodextrins: α- cyclodextrin, .beta.-cyclodextrin and γ- cyclodextrin. The term "cyclodextrin" also includes various substituted cyclodextrins, including as side chains any organic moiety or a heteroorganic moiety. Substituted cyclodextrins also include cyclodextrins that have been alkylated, hydroxyalkylated, or reacted to form a sulfoalkyl ether.

SUMM As used herein, cyclodextrins and/or substituted cyclodextrins include, but are not limited to, sulfobutylether cyclodextrin, hydroxypropyl cyclodextrin, hydroxyethyl cyclodextrin, glucosyl cyclodextrin, maltosyl cyclodextrin, hydroxypropyl-.beta.-cyclodextrin, sulfobutylether-.beta.-cyclodextrin, hydroxyethyl-.beta.-cyclodextrin, hydroxypropyl-γ- cyclodextrin, hydroxyethyl-.beta.-cyclodextrin, dihydroxypropyl-.beta.-cyclodextrin, glucosyl-.beta.-cyclodextrin, diglycosyl-.beta.-cyclodextrin, maltosyl-.beta.-cyclodextrin, maltosyl-γ-cyclodextrin, maltotrialsyl-.beta.-cyclodextrin, maltotrialsyl-γ- cyclodextrin, dimaltosyl-.beta.-cyclodextrin, cyclodextrin derivatives, various mixtures of cyclodextrin derivatives thereof, mixtures such as maltosyl-.beta.-cyclodextrin/dimaltosyl-.beta.-cyclodextrin, and any other similar cyclodextrin known to those of skill in the art.

DETD . . . of the compound of Formula I or Ia may also be used, such as the citrate or malate salts. A cyclodextrin may be added to the solution in a concentration range of about 2% to about 40%. Preferably, the cyclodextrin comprises about 5% to about 20%

of the pharmaceutical composition and more preferably about 5% to about 10%. Pharmaceutical compositions comprising the compound of I or Ia, cyclodextrin and a pharmaceutically acceptable preservative are described in co-pending U.S. provisional application No. 60/540,897 assigned to and owned by Pfizer, Inc. A method of improving. . .

DETD . . . solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers or diluents (including solvents and vehicles) include water, ethanol, polyols (propylene glycol, polyethylene glycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oils) and injectable organic esters, such. . .

DETD . . . solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (e.g., cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil, sesame seed oil and. . .

CLM What is claimed is:

19. The method or use according to claim 18 wherein said composition further comprises a pharmaceutically acceptable cyclodextrin.

IT 147116-67-4 147116-68-5 862543-54-2 863879-43-0
863879-44-1 863879-45-2 863879-46-3
(NK-1 receptor antagonists for anesthesia recovery)
IT 12619-70-4, Cyclodextrin
(NK-1 receptor antagonists for anesthesia recovery)
INCL INCLM: 514/305.000
NCL NCLM: 514/305.000
IC IPCI A61K0031-4745 [I,A]; A61K0031-4738 [I,C*]
IPCR A61K0031-4738 [I,C]; A61K0031-4745 [I,A]

CHEMICAL ABSTRACTS INDEXING COPYRIGHT 2009 ACS on STN

	PATENT	KIND	DATE
OS CA 143:279425 *	WO 2005082366	A1	20050909

* CA Indexing for this record included
CC 1-11 (Pharmacology)
ST anesthesia recovery NK1 receptor antagonist; quinuclidine deriv NK1 receptor antagonist anesthesia recovery
IT Anesthesia
Drug delivery systems
(NK-1 receptor antagonists for anesthesia recovery)
IT Tachykinin antagonists
(NK1 receptor antagonists; NK-1 receptor antagonists for anesthesia recovery)
IT Drug delivery systems
(enteric; NK-1 receptor antagonists for anesthesia recovery)
IT Drug delivery systems
(oral; NK-1 receptor antagonists for anesthesia recovery)
IT Drug delivery systems
(parenterals; NK-1 receptor antagonists for anesthesia recovery)
IT Drug delivery systems
(prodrugs; NK-1 receptor antagonists for anesthesia recovery)
IT 147116-67-4 147116-68-5 862543-54-2 863879-43-0
863879-44-1 863879-45-2 863879-46-3
(NK-1 receptor antagonists for anesthesia recovery)
IT 12619-70-4, Cyclodextrin
(NK-1 receptor antagonists for anesthesia recovery)

L20 ANSWER 3 OF 6 USPATFULL on STN
ACCESSION NUMBER: 2007:177876 USPATFULL
TITLE: Antimicrobial preservatives to achieve multi-dose formulation using beta-cyclodextrins for liquid dosage forms
INVENTOR(S): Adami, Roger C., Snohomish, WA, UNITED STATES
David, Frederick, Kent, UNITED KINGDOM
Wood, Julia Ann, Sprague, CT, UNITED STATES
PATENT ASSIGNEE(S): Pfizer Inc. (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20070155697	A1	20070705	
APPLICATION INFO.:	US 2005-588070	A1	20050117	(10)
	WO 2005-IB100		20050117	
			20061213	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 2004-540897P	20040130 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PHARMACIA & UPJOHN, 7000 Portage Road, KZO-300-104, KALAMAZOO, MI, 49001, US
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1-10
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 1510
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Antimicrobial preservatives to achieve multi-dose formulation using beta-cyclodextrins for liquid dosage forms

AB . . . invention is directed to pharmaceutical compositions containing a therapeutically effective amount of an Active Pharmaceutical Ingredient ("API"), a pharmaceutically acceptable cyclodextrin and a pharmaceutically acceptable preservative. The invention is also directed to pharmaceutical compositions of the compounds of Formula (I) wherein R.sup.2 is selected from the group consisting of methyl, ethyl, isopropyl, sec-butyl and tert-butyl and a pharmaceutically acceptable cyclodextrin and preservative. Formula (I): In particular, the invention is directed to pharmaceutical compositions of the compound of Formula 1a, and a pharmaceutically acceptable cyclodextrin and a preservative. ##STR1##

SUMM . . . invention is directed to pharmaceutical compositions containing a therapeutically effective amount of an Active Pharmaceutical Ingredient ("API"), a pharmaceutically acceptable cyclodextrin and a pharmaceutically acceptable preservative. The invention is also directed to pharmaceutical compositions of the compounds of Formula I, wherein R.sup.2 is selected from the group consisting of methyl, ethyl, isopropyl, sec-butyl and tert-butyl and a pharmaceutically acceptable cyclodextrin and preservative. ##STR2##

SUMM In particular, the invention is directed to pharmaceutical compositions of the compound of Formula Ia, and a pharmaceutically acceptable cyclodextrin and a preservative. ##STR3##

SUMM . . . improving injection site toleration of injectable aqueous solutions comprising the compound of Formula I, or its pharmaceutically acceptable salts, a .beta.-cyclodextrin and a preservative.

SUMM . . . salts (e.g. NaCl, CaCl.sub.2 or sodium acetate), using a partially-aqueous, oleaginous, or micellar vehicle, or adding a modified, parenterally acceptable cyclodextrin. Generally, however, it was observed that formulations containing cyclodextrins provided improved injection site toleration over other approaches to increasing solubility.

SUMM Cyclodextrin may enhance solubility by forming an inclusion complex with the drug molecule whereby the insoluble/hydrophobic drug is inserted into the hydrophobic cavity of the cyclodextrin. The outer hydrophilic shell of the cyclodextrin molecule then enhances solubility of the entire complex. Standard terminology for cyclodextrin complexation identifies the cyclodextrin as a "host" molecule and the drug as a "guest" molecule. Unfortunately, the cyclodextrin used to form the inclusion complex may also bind preservatives, inactivating many poorly water-soluble preservatives.

SUMM Sulfobutylether-.beta.cyclodextrin (hereinafter "SBE-CD") was found to be effective at both increasing the solubility of compound of Formula Ia and ameliorating injection site reactions. Unfortunately, investigation determined that SBE-CD formed complexes with both antimicrobial preservative (e.g. meta-cresol) and the compound of Formula Ia, resulting in competitive binding interactions and, in general, antimicrobial ineffectiveness.

SUMM Consequently, it was necessary to obtain an optimal balance between a sufficient concentration of cyclodextrin (e.g., SBE-CD) and antimicrobial preservative (e.g. meta-cresol). While a lower concentration of SBE-CD would increase antimicrobial preservative efficacy, this advantage would be offset, however, by a decrease in acceptable injection site toleration ("IST"). These competing performance characteristics necessitated balancing antimicrobial preservative efficacy (criteria A) and acceptable injection-site-toleration for the product.

SUMM . . . method of improving injection site toleration during the parenteral administration of a composition containing the compound of Formula I and cyclodextrin. A cyclodextrin -compatible preservative was also identified, providing desirable multi-use dosing options. Preferably, meta-cresol is used in the formulation to prevent bacterial and fungal development in the formulation during the proposed extended in-use period.

SUMM . . . the invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of an Active Pharmaceutical Ingredient (API), a .beta.-cyclodextrin , a pharmaceutically acceptable preservative, a pharmaceutically acceptable vehicle, and an optional pharmaceutically acceptable excipient, wherein the preservative demonstrates pharmaceutically acceptable antimicrobial preservative effectiveness.

SUMM In a preferred embodiment, the .beta.-cyclodextrin is 2-hydroxypropyl-.beta.-cyclodextrin or sulfobutyl ether-.beta.-cyclodextrin, preferably sulfobutyl ether-.beta.-cyclodextrin.

SUMM In another embodiment, the pharmaceutically acceptable preservative is selected from thimerosal, propylene glycol, phenol, or meta-cresol or a combination thereof. Preferably the preservative is meta-cresol. Preferably, the concentration of preservative is about 0.1 mg/mL to about 600 mg/mL. Preferably, the preservative is meta-cresol and is in

a concentration of about 0.1 mg/mL to about 20 mg/mL.

SUMM In a preferred embodiment, the preservative has a binding value to the cyclodextrin that is less than a binding value of the API to cyclodextrin. Preferably, the binding value of the API to cyclodextrin is between 500 M.sup.-1 and 10,000 M.sup.-1. Preferably, the binding value of the API to cyclodextrin is between 800 M.sup.-1 and 3,000 M.sup.-1.

SUMM In another embodiment, the Active Pharmaceutical Ingredient has a greater than or equal to two-fold binding constant with cyclodextrin over that of the preservative. In a preferred embodiment, the binding constant is greater than or equal to five-fold. In a more preferred embodiment, the. . .

SUMM In a preferred embodiment, about 1 mg/mL to about 5 mg/mL of the preservative, preferably meta-cresol, is unsequestered in the cyclodextrin. Preferably, about 2.5 mg/mL of the preservative, preferably meta-cresol , is unsequestered in the cyclodextrin.

SUMM . . . wherein R.sup.2 is selected from the group consisting of methyl, ethyl, isopropyl, secbutyl and tertbutyl, preferably tert-butyl, a pharmaceutically acceptable .beta.-cyclodextrin, a pharmaceutically acceptable preservative, a pharmaceutically acceptable vehicle and an optional pharmaceutically acceptable excipient.

SUMM Preferably, the .beta.-cyclodextrin is 2-hydroxypropyl-.beta.-cyclodextrin or sulfobutyl ether-.beta.-cyclodextrin , preferably sulfobutyl ether-.beta.-cyclodextrin.

SUMM Preferably, the pharmaceutically acceptable preservative is selected from thimerosal, propylene glycol, phenol, or meta-cresol, or a combination thereof. Preferably, the preservative is meta-cresol.

SUMM In a preferred embodiment, about 1 mg/mL to about 5 mg/mL of the preservative, e.g. meta-cresol, is unsequestered in the cyclodextrin.

SUMM . . . or a pharmaceutically acceptable salt thereof, is in an amount of about 0.1 mg/mL to about 100 mg/mL and the .beta.-cyclodextrin is in an amount of about 20 mg/mL to about 200 mg/mL and the preservative is meta-cresol. Preferably, the .beta.-cyclodextrin is in the amount of 55 mg/mL to 100 mg/mL and the meta-cresol is an amount of about 2.5 mg/mL to 3.5 mg/mL.

SUMM . . . or a pharmaceutically acceptable salt thereof, is in an amount of about 0.1 mg/mL to about 100 mg/mL and the .beta.-cyclodextrin is in an amount of about 20 mg/mL to about 200 mg/mL and the preservative is meta-cresol and is in an amount of about 1 mg/mL to about 5 mg/mL. Preferably, the .beta.-cyclodextrin is in an amount of about 55 mg/mL to about 100 mg/mL and the preservative is meta-cresol and is in an amount of about 2.5 mg/mL to about 3.5 mg/mL. Preferably, the .beta.-cyclodextrin is sulfobutyl ether-.beta.-cyclodextrin .

SUMM . . . the compound of Formula Ia, ##STR6## or its pharmaceutically acceptable salts, wherein the compound of Formula Ia is 10 mgA/mL, sulfobutyl ether-.beta.-cyclodextrin is in an amount of about 63 mg/mL and meta -cresol is in an amount of about 3.3 mg/mL, a pharmaceutically acceptable vehicle and an optional pharmaceutically acceptable

excipient. Preferably, the. . .

SUMM . . . mammal an aqueous pharmaceutical composition comprising the above described pharmaceutical compositions of the compounds of Formula I or Ia, the .beta.-cyclodextrin being present in amounts which are sufficient for improved injection toleration at the injection site. Preferably, the pharmaceutically acceptable salt. . .

SUMM . . . is directed to a method to develop a preserved API compositions comprising a therapeutically effective amount of an API, a .beta.-cyclodextrin and a pharmaceutically acceptable preservative.

SUMM In a preferred embodiment, the preservative has a binding value to the cyclodextrin that is less than a binding value of the API to cyclodextrin. Preferably, the preservative is selected from thimerosal, propylene, glycol, phenol or meta-cresol or a combination thereof.

SUMM In a preferred embodiment, the binding value of the API with the cyclodextrin is greater than 50 M.sup.-1. Preferably, the binding value of the API with the cyclodextrin is between 500 and 10,000 M.sup.-1. Preferably, the binding value of the API with the cyclodextrin is between 800 and 3,000 M.sup.-1.

SUMM . . . herein refers to a pharmaceutical drug substance having therapeutic properties and having the ability to bind or be "sequestered" in cyclodextrin. Preferably, the API has a binding value to cyclodextrin greater than 50 M.sup.-1. More preferably, the API has a binding value to cyclodextrin between about 800 M.sup.-1 to about 3,000 M.sup.-1. Even more preferably, the API has a binding value to cyclodextrin between about 500 M.sup.-1 to about 10,000 M.sup.-1. Furthermore, preferably, the API has greater than a two-fold binding constant with cyclodextrin over preservative. More preferably, the API has a greater than 5 fold binding constant with cyclodextrin. Even more preferably, the API has greater than or equal to 10 fold binding constant with cyclodextrin.

SUMM The term "cyclodextrin" refers to a compound including cyclic alpha (1→4) linked D-glucopyranose units. α-cyclodextrin refers to a cyclodextrin with 6 cyclic, linked D-glucopyranose units, .beta.-cyclodextrin has 7 cyclic, linked D-glucopyranose units, and .beta.-cyclodextrin has 8 cyclic, linked D-glucopyranose units. These cyclic, linked D-glucopyranose units define a hydrophobic cavity, and cyclodextrins are known to form inclusion compounds with other organic molecules, with salts, and with halogens either in the solid state. . .

SUMM Cyclodextrins vary in structure and properties. For example, the size (e.g. diameter, and depth) and functionality (e.g. hydrophobicity, charge, reactivity and ability to hydrogen bond) of the hydrophobic cavity varies among substituted and unsubstituted α-, β- and γ- cyclodextrins. Typically, a cyclodextrin selected for a formulation has a size and functionality that binds with the target component the other components of the formulation. For the present formulations and methods, it is believed that substituted cyclodextrins, such as hydroxyalkyl cyclodextrins and sulfoalkylether cyclodextrins have a size and functionality that compliment the other components of the formulation. Preferred cyclodextrins include hydroxypropyl-.beta.-cyclodextrin and sulfobutylether-.beta.-cyclodextrin. More preferably, the cyclodextrin is sulfobutylether-.beta.-cyclodextrin ("SBE-CD").

SUMM The term "pharmaceutically acceptable preservative," as used

herein, means a preservative. In particular, the formulation containing preservative maintains effectiveness according to the standards set forth in Ph. Eur. 4.sup.th Ed. 2003 (5.1.3) for parenteral formulations and USP26 NF21S2, <51 > for Category 1 pharmaceutical products. Preferably, the preservative has a reduced binding value to cyclodextrin compared to the API, such that the sufficient preservative is "unsequestered" in the cyclodextrin, providing effective antimicrobial effectiveness.

DRWD FIG. 1 depicts the saturated meta-cresol solutions of SBE-CD and compound of Formula Ia. Meta-cresol concentration showed linear increase as SBE-CD was increased. The concentration of drug did not significantly alter the solubility of m-cresol in SBE-CD.

DRWD FIG. 3 depicts the comparison between bacterial efficacy as a function of total quantity of meta-cresol and as a function of calculated sequestered meta-cresol for S. aureus at 6 hours and 24 hours time points.

DRWD FIG. 4 depicts a formulation window to guaranty preservative effectiveness according to Ph. Eur. Criteria A, no pain on injection, less than 3.5 mg/mL meta-cresol, and less than 80 mg/mL SBE-CD.

DETD Development of parenteral formulations utilizing cyclodextrin for solubilization, or for other purposes, requires an understanding of the interaction between the drug and cyclodextrin. A pharmaceutical drug that is solubilized by cyclodextrin is bound at a stoichiometric relationship related to an inherent binding constant. This relationship varies based on several factors such as the structure of the drug, cyclodextrin, and solution properties (e.g., pH, ionic strength, and cosolvency).

DETD Formulations having multiple excipients further complicate the interaction. For example, in parenteral multi-use formulations containing a preservative, the preservative may compete with the drug for cyclodextrin binding. It was previously reported that 2-hydroxypropyl-.beta.-cyclodextrin interacts not only with drug molecules but can also form complexes with antimicrobial preservatives. Loftsson, T. et al.,. Drug Development and Industrial Pharmacy 1992, 18(13), 1477-1484.

DETD Binding of the preservative and cyclodextrin, however, decreases the antimicrobial effectiveness of the preservative, since the preservative needs to be unbound in solution. A minimum requirement for the efficacy of the preservation for parenteral products is described in the European Pharmacopoeia, criteria A being applicable, and in the U.S. Pharmacopoeia. Antimicrobial Preservatives for proposed formulations were evaluated pursuant to the Antimicrobial Effectiveness Testing ("AET") criteria.

DETD A multi-dose formulation of the compound of Formula Ia containing 10 mgA/mL compound of Formula Ia and 10% (w/v) cyclodextrin at pH 4.4 was utilized to identify an efficacious antimicrobial preservative that did not significantly interact with cyclodextrin. From preliminary experiments, the solubility of the compound of Formula I in the presence of 2-hydroxypropyl-.beta.-cyclodextrin was similar to the solubility in the presence SBE-CD. Furthermore, both yielded a formulation with acceptable injection site toleration ("IST"). In addition to compatibility with cyclodextrin, e.g. SBE-CD, there was additional criteria that limited the antimicrobial preservatives acceptable for the formulation. These criteria

were physical and chemical compatibility with compound of Formula Ia; preservative effectiveness against bacteria, molds, and yeasts at pH of about 4.4 and acceptable injection site toleration.

DETD As discussed more fully in the Experimental section, a preliminary screen for an antimicrobial preservative for the multidose compound of Formula Ia formulation was conducted with chlorocresol, phenyl ethanol, benzyl alcohol, ethanol, bronopol, sucrose, chlorhexidine gluconate, thimerosal, benzethonium chloride, benzalkonium chloride, chlorobutanol, benzoic acid, meta-cresol, phenol, and 25% propylene glycol. Initial results indicated that thimerosal, chlorobutanol/phenylethanol, ethanol and propylene glycol (50%) satisfied USP/Ph. Eur. requirements (Table VII).

DETD When considering injection site toleration issues, chlorobutanol/phenylethanol, ethanol and propylene glycol demonstrated poor injection site toleration (Table VIII). Conversely, thimerosal and meta-cresol provided good injection site toleration.

DETD Benzethonium chloride and benzoic acid were both ineffective at reducing the microorganisms after 7 days. Propylene glycol (25%) was active against bacteria only in the presence of SBE-CD, but ineffective against the fungi. On the other hand, the phenolic compounds, phenol and meta-cresol were effective at reducing the microorganisms, but their activity against bacteria was greatly diminished when SBE-CD was present in the. . .

DETD . . . by the inventors, that the difficulties encountered to preserve the desired formulation were due to an interaction between the antimicrobial preservative (e.g. meta-cresol) and the SBE-CD. In particular, preservative, for example meta-cresol, was likely sequestered by SBE-CD, rendering the meta-cresol inactive against bacteria and fungi. In order to demonstrate this theory, the binding constant of compound of Formula Ia to SBE-CD and meta-cresol to SBE-CD were determined (K.sub.p). These constants were used to calculate the concentration of non-sequestered meta-cresol in the formulations tested for anti-microbial efficacy. The average values used for calculations are binding constant for drug ("K.sub.D"=1000) and binding constant for preservative ("K.sub.p"=28).

DETD . . . measured using techniques such as spectroscopy, or calorimetry. Gadre, A., and Connors, K. A. "Binding of Substituted Acetic Acids to α- Cyclodextrin in Aqueous Solution" J. Pharm. Sci. 1997 86(11):1210-1214.). In order to differentiate inclusion binding from other possible solubilization effects of. . . agent, such as stacking or hydrotropy, a method is required to determine the binding constant of one component bound to cyclodextrin in the presence of other competitive binders. The ability to distinguish between binding and other modes of interaction is significant. . .

DETD . . . method to determine binding constants utilizes equilibrium dialysis in the development of a multi-use parenteral formulation containing SBE-CD and a preservative. In particular, the method was applied in developing a parenteral formulation comprising the compound of Formula Ia, a cyclodextrin (SBE-CD) and a preservative (meta-cresol). This approach is applicable to compounds other than the compound of Formula Ia in developing parenteral formulations and is within the scope of this invention. Development of the formulation using this approach resulted in optimization of cyclodextrin bound drug and unbound preservative. The significance of this procedure is its ability to measure the binding constant of multiple compounds competing for

binding with the cyclodextrin. The experimental dialysis data also provides an easily interpreted representation of binding in the formulation by visualizing the degree of. . .

DETD . . . equilibrate over time with an acceptor compartment. Ono, N., Hirayama, F., Arima, H., Uekama, K. "Determination of Stability Constant of .beta.-Cyclodextrin Complexes Using the Membrane Permeation Technique and the Permeation Behavior of Drug Competing Agent-.beta.-Cyclodextrin Ternary Systems" Eur. J. Pharm. Sci. 1999 9:133-139. The acceptor cell contains no ligand. The membrane is semi-permeable allowing the typically low molecular weight substrates to freely diffuse, while the cyclodextrin (MW=2163) remains in the donor compartment. Sampling from both compartments over time yields a time-concentration profile of substrate in both. . .

DETD . . . the competitive binding that occurs in the solution. The equilibrium binding constant is a measure of the relative concentration of meta-cresol bound to SBE-CD according to the chemical equilibrium equation below: S=meta-cresol, L=SBE-CD. S:L indicates the complex formed between meta-cresol and SBE-CD. ##EQU1## Solubility Analysis.

DETD . . . solution. Traditional solubility methods were performed initially to determine the solubility and binding constants of compound of Formula Ia and preservative with SBE-CD. These studies allowed determination of the stoichiometry of binding between SBE-CD and compound of Formula Ia as seen. . .

DETD Binding was calculated for meta-cresol using solubility analysis. The experiment was performed at different concentrations of compound of Formula Ia to determine if there was any effect from the presence of drug in solution on the meta-cresol binding constant. Meta-cresol solubility was measured in excess (saturated) meta-cresol and the equilibrium binding constant was calculated using the following equation: ##EQU2## Where S.sub.t is the total solubility of meta-cresol, s.sub.0 is the inherent solubility of meta-cresol, L.sub.t is the total concentration of SBE-CD (ligand) and K.sub.11 is the equilibrium binding constant of meta-cresol assuming a 1 to 1 binding stoichiometry.

DETD Applying the solubility method, the equilibrium binding constant of meta-cresol averaged 27.6 M.sup.-1 across the studies. There was minimal effect on the binding from the presence of compound of Formula. . . investigated. Compound of Formula Ia had a binding constant of 1040 M.sup.-1 at pH 4.4.

TABLE I

Calculated binding constants from meta-cresol saturated solubility experiments in varying SBE-CD and drug (compound of Formula Ia). The slope of meta-cresol solubility vs. SBE-CD concentration was used to estimate binding. The addition of compound of Formula la did not significantly alter meta-cresol concentration.

Compound of Formula Ia [mM]	Slope	y-intercept [mM]	R.sup.2	K.sub.11 (equilibrium)
00.00	0.46	34.06	0.88	24.53
10.67	0.46	33.15	0.95	25.78
21.34	0.53	32.15. . .		

DETD The initial experiments established the equilibrium dialysis flux rates for compound of Formula Ia and meta-cresol across the 500 MWCO dialysis membrane. Three different concentrations of

compound of Formula Ia were initially loaded into the donor. . . dialysis method.

Asymptotic diffusion rates were fit to equation 11 using numerical line-fitting software to generate binding constants.

Approximate Ratio	Compound of Formula Ia [mM]	Meta-cresol [mM]	SBE-CD k (hr.sup.-1)	K.sub.eq [M.sup.-1]
1:1	1.0	1.0	0.015	740
1:2	0.5	1.0	0.013	1092
1:4	0.25	1.0	0.012	1444

1:1. . .

DETD . . . [D].sub.A are free drug in the donor well and free drug in the acceptor well, respectively. The mass balance for cyclodextrin in the system, maintained within the donor phase, is given below: [CyD].sub.tot=[CyD].sub.F+[D:CyD] (5) Substituting the complexed drug from the mass. . .

DETD Using the cyclodextrin mass balance and solving for free cyclodextrin in terms of known values gives: CyD.sub.F=CyD.sub.tot-D.sub.tot+D.sub.F+D.sub.A (9) Replacing free drug, D.sub.F, by its equilibrium relationship leads to: ##EQU8## Solving the quadratic for free cyclodextrin, CyD.sub.F provides: ##EQU9##

DETD . . . method was 1092 M-1 (±352 M-1, n=3), compared to 1040 M-1 (n=1) for the solubility method. The binding constant for preservative and SBE-CD, using the solubility method was 28 M-1 (n=1) compared to 83 M-1 (±7 M-1) using equilibrium dialysis. The data demonstrates that, in binary systems, both drug (e.g., compound of Formula Ia) and preservative bind to the cavity in SBE-CD, although in this case the drug binding constant was 13-fold greater than preservative. The data showed that in ternary systems comprised of SBE-CD, drug (e.g., compound of Formula Ia), and preservative , at the ratios tested, the equilibrium profile indicated that the preservative was not bound to cyclodextrin due to competitive binding with the drug.

DETD Based upon the above calculations to obtain the amount of sequestered meta-cresol and compound of Formula Ia, proposed formulations were developed and evaluated for antimicrobial efficacy. FIG. 3 demonstrates no clear relationship between the total meta -cresol concentration contained in the formulation and the log reduction of bacterial population, 6 or 24 hours after spiking a known amount of Staphylococcus Aureus (i.e. formulations containing about 3 mg/mL meta-cresol seem to equally have a log reduction as low as 0 or as high as greater than 4.6). When the same data set is plotted against the calculated non-sequestered meta -cresol concentration in the formulation, (FIG. 4) however, a relationship is visible. This data set was produced with a number of formulations containing 9.0 to 11.0 mgA/mL of compound of Formula Ia, 2.5 to 4.75 mg/mL meta-cresol and 60 to 100 mg/mL SBE-CD. The appearance of a plateau at the higher concentrations is only due to the limitation in the bactericidal efficacy measurement method. As the method consists in evaluating the population not killed by the preservative, when the whole population is dead (i.e. none is detectable any more .about.100%) the figure quoted is of the form:. . .

DETD Two additional parameters were: (1) the level of total meta- cresol concentration; and (2) the level of cyclodextrin (e.g., SBE-CD) should be kept as low as possible and, in particular, below 80 mg/mL to prevent binding to and inactivating meta-

cresol. (See FIG. 4). Accordingly, formulations containing 9.0 to 11.0 mgA/mL of compound of Formula I, 2.5 to 4.75 mg/mL meta-cresol and 60 to 100 mg/mL SBE-CD were designed to contain known amount of calculated non-sequestered compound of Formula I and known calculated amount of non-sequestered meta-cresol. The formulations were analyzed for preservative effectiveness. These results are reported in FIG. 4. From these results a limit of confidence in robust preservative effectiveness was defined and reported on FIG. 4.

DETD Based on these results, the preferred formulation containing calculated non-sequestered concentrations of meta-cresol (2.8 mg/mL) and compound of Formula I (1.4 mg/mL), corresponding to the black diamond on FIG. 4, was selected. This. . . formulation corresponded to actual total concentrations of 10 mgA/mL of compound of Formula I, 63 mg/mL SBE-CD and 3.3 mg/mL meta-cresol at pH 4.4.

DETD . . . the citrate salt of compound of Formula Ia are applicable in the development of other parenteral formulations comprising pharmaceutical drugs, cyclodextrin and preservative. In particular concentrations of drug, cyclodextrin and preservative should be adjusted to have minimum concentration of non sequestered preservative (2.1 mg/ml when using metacresol).

DETD . . . acceptable salt of the compound of Formula I may also be used, such as the citrate or malate salts. A cyclodextrin is added to the solution in a concentration range of about 2% to about 40%. Preferably, the cyclodextrin comprises about 5% to about 20% of the pharmaceutical composition and more preferably about 5% to about 10%. Preferably, the cyclodextrin is a .beta.-cyclodextrin: hydroxypropyl .beta.-cyclodextrin, sulfobutylether .beta.-cyclodextrin or other pharmaceutically acceptable substituted .beta.-cyclodextrin. A preservative is added to the formulation on a weight basis.

DETD . . . is 10 mgA/mL compound of Formula Ia as the citrate monohydrate salt, about 63 mg/mL SBE-CD, and about 3.3 mg/mL meta-cresol at pH 4.4.

DETD Materials. Meta-cresol (MW=108.14) was obtained from Aldrich, St. Louis, Mo. A 20-cell equilibrium dialyzer, equipped with 2 mL Teflon cells and 500. . .

DETD . . . of Formulations. Three different test formulations were prepared composed of either single component controls; binary systems containing either drug or m-cresol, and SBE-CD; or ternary systems containing drug, m-cresol, and SBE-CD. Formulations were prepared at room temperature at different ratios and concentrations 24 hrs prior to testing to assure equilibrium binding. The formulations were prepared by first dissolving SBE-CD at the appropriate concentration and then adding drug or m-cresol and allowing it to dissolve in the cyclodextrin solution.

DETD Control Experiments. The dialysis rates of compound of Formula Ia and meta-cresol were measured alone across the 500 MWCO membrane. Different concentrations of meta-cresol and compound of Formula Ia were placed on the donor side of the equilibrium dialyzer. The concentrations of corresponding complexation experiments were chosen to match the concentration of drug or preservative in the single component systems.

DETD Binary Systems. These experiments were performed to quantify the binding of either drug or m-cresol with SBE-CD. Three separate mixtures were tested which consisted of: compound of Formula Ia with SBE-CD, meta-cresol with SBE-CD, and

drug with meta-cresol. The molar ratios of SBE-CD to drug or preservative were 1:1, 2:1, and 4:1.

DETD . . . Several experiments were performed to test the effects of all three formulation components on the dialysis rate of drug and preservative. In these, SBE-CD concentration was fixed while the amounts/ratios of compound of Formula Ia and meta-cresol were varied.

DETD C. Antimicrobial Preservatives Evaluated for Pharmaceutical Compositions

DETD Table III summarizes the antimicrobial preservatives evaluated for use in the formulation. Each antimicrobial preservative was tested at the highest concentration currently used in commercial products. The antimicrobial preservatives were purchased from general chemical sources.

TABLE III

Antimicrobial Preservatives Screened

Antimicrobial preservative	Percent (w/v)	pH
Phenol	0.5%	4.4
meta-cresol	0.3%	4.4
meta-cresol + EDTA	0.5% meta-cresol + 0.15% edta	4.4
Chlorocresol	0.1%	4.4
Chlorocresol + EDTA	0.1% + 0.15% edta	4.4
Chlorobutanol	0.5%	3.5
Chlorobutanol & Phenylethanol	0.5% each	3.5
Chlorobutanol. . . w/ Titration of Phenylethanol**	3.5	
Phenylethanol	0.5%	3.5
Thimerosal	0.01%	4.4
Benzoic Acid	0.2%	3.5
Benzethonium chloride	0.02%	4.4
Benzalkonium chloride	0.01%	4.4
Benzyl alcohol	2.0%	4.4
Propylene glycol	25%	4.4
Ethanol	15%	4.4
Bronopol	0.1%	5.0
Sucrose	50%	4.4
Chlorhexidine gluconate	0.5%	5.0

**Titration of Phenylethanol from 0.5-0.1% in 0.1% increments

DETD Preparation of Preserved Formulations. Formulations were prepared, where solubility permitted, at 5% and 10% (weight/volume) SBE-CD. Antimicrobial preservatives with optimal activity at a pH outside the nominal formulation value (pH 4.4) were titrated to either 3.5 or 5.0. . . solution of either 10% or 5% (weight/volume) SBE-CD containing 10 mgA/mL of the compound of Formula Ia citrate was prepared. Preservative was added to the respective formulation on a weight basis.

DETD . . . inoculated product was transferred into 9 mL of a recovery diluent, that was validated to confirm neutralization of the antimicrobial preservative. One mL of the diluted sample was then transferred to a sterile petri dish and combined with 15-20 mL of. . .

DETD . . . formulations were evaluated under various accelerated

stability conditions in order to assess potency and purity of compound of Formula Ia, preservative content and SBE-CD content. For example, in one accelerated stability study, potential lead formulations were placed in stability ovens to. . . 50° C., 30° C., and 5° C. temperature chambers and analyzed for compound of Formula Ia potency and purity, antimicrobial preservative and SBE-CD content, at 1, 3, 6, and 12-week time intervals. Purity and potency assays to measure compound of Formula Ia, as well as antimicrobial preservatives and SBE-CD content, were performed using validated HPLC methodology. SBE-CD was assayed using GTP 5984.

DETD . . . general, formulations not containing SBE-CD were, generally, poorly tolerated. Formulations consisting of 10 mgA/mL compound of Formula Ia, 10% excess meta-cresol (0.33% w/v) and about 6.8% to 7.6% SBE-CD were evaluated for IST. In particular, formulations containing 10 mgA/mL compound of Formula Ia, 61 to 72 mg/mL SBE-CD and 3.2 to 4.2 mg/mL meta-cresol were tested for injection site toleration and all were well tolerated.

DETD Selection of Antimicrobial Preservatives for Injectable Compound of Formula Ia

DETD Study A (Large Antimicrobial Preservative Screen)

DETD The efficacy of several different antimicrobial preservatives in combination with compound of Formula Ia and SBE-CD were investigated. Literature indicated that the antimicrobial preservatives that met both the USP and either Ph. Eur. criteria A or B requirements were ethanol, propylene glycol, benzoic acid, thimerosal, meta-cresol, (Lucchini, J. J.; Corre, J.; and Cremieux, A. "Antibacterial activity of phenolic compounds and aromatic alcohols" Res. Microbiol. 141, 499-510,. . .

DETD Table VII sets forth results for screening various antimicrobial preservatives or combinations thereof.

TABLE VII

ANTIMICROBIAL EFFECTIVENESS TESTING:
SCREEN FOR ANTIMICROBIAL PRESERVATIVE SYSTEM

ANTIMICROBIAL PRESERVATIVE	FORMULATION DESCRIPTION	ACCEPTABLE STABILITY	AET RESULTS AGAINST COMPENDIA USP	Ph. Eur. Criteria A	Ph. Eur. Criteria B
Benzalkonium Chloride (0.01%)	pH 4.4 10% SBE-CD	Not Tested			
Benzalkonium (15%)	pH 4.4 5% SBE-CD	Not Tested	.check. . . 4.4 .check mark.	.check mark.	.check mark.
Ethanol (30%)	pH 4.4 5% SBE-CD	Not Tested	.check mark.	.check mark.	.check mark.
meta-cresol (0.3%)	pH 4.4 10% SBE-CD	.check mark.		.check mark.	
meta-cresol (0.3%)	pH 4.4 8% SBE-CD	Not Tested		.check mark.	
meta-cresol (0.3%)	pH 4.4 9% SBE-CD	Not Tested		.check mark.	
Phenol	pH 4.4	.check mark.	.check		

mark. .check mark.
(0.5%) 10% SBE-CD
Phenylethanol pH 3.5 Not Tested
(0.5%) 10% SBE-CD
Propylene Glycol pH 4.4 Not Tested
.check mark.
(25%) 10% SBE-CD
Propylene Glycol pH 4.4 Not Tested
.check mark.
(25%) 5% SBE-CD
Propylene Glycol pH 4.4 Not Tested
.check mark. .check mark. .check mark.
(50%) 5% SBE-CD
Sucrose pH 4.4 Not Tested
(50%) 5% SBE-CD
Thimerosal pH 4.4. . .

DETD Formulations containing these antimicrobial preservatives were further evaluated for physical and chemical stability and injection site toleration. (See Table VII). The co-solvent antimicrobial preservative approaches, ethanol and propylene glycol, failed to satisfy acceptable IST. Furthermore, benzoic acid formulations also provided poor IST results.

TABLE VIII

Results of Study A

Antimicrobial preservative Formulation*	Content (Actual/ Precedence)	IST	Stability	AET Results USP	Ph. Eur. Criteria A	Ph. Eur. Criteria B
Benzoic acid (6,. . . aur (6 hr)	0.2%/0.2%	Poor	OK	.check mark.	s. aur .check mark.	
pH: 4.4 SBE-CD: 10%						
Ethanol (7 d)	15%/70% .check mark.	Poor	OK 1 w/70	.check mark.	a. niger	
pH:4.4 SBE-CD: 5%						
meta-cresol .check mark.	0.3%/0.3%	Good	OK 12 w/70 C.	.check mark.	c. alb (7 d)	
pH: 4.4 SBE-CD: 10%	s. aur (6, 24 hr)					
Propylene glycol .check mark.	50%/40% .check mark.	Poor	NT .check mark.			
pH: 4.4 SBE-CD: 10%						
Thimerosal mark.	0.01/0.01% .check. . . 10 mgA/mL	Good	1 wk/70	.check mark.	.check	

.check mark. denotes USP and/or Ph. Eur. Criteria satisfied.

Study B (Ph. Eur. Criteria B Meeting Antimicrobial Preservative Screen)

DETD All antimicrobial preservatives that met Ph. Eur. criteria B were further screened for injection site toleration and stability. The leads identified in Table VII and Table IX that met criteria B were thimerosal, meta-cresol, and benzoic acid. These

formulations were evaluated for stability and IST (Table VII).

DETD On the other hand, meta-cresol containing formulations exhibited excellent stability and injection site toleration. Accordingly, meta-cresol was identified as the preferable antimicrobial preservative due to excellent injection site tolerability, as well as robustly meeting Ph. Eur. criteria A for preservative efficacy. Because of these favorable performance characteristics, the formulation was optimized with respect to SBE-CD concentration, resulting in a formulation with a high margin of solubility, robust antimicrobial preservative efficacy, and acceptable injection site toleration.

DETD The stability of meta-cresol and compound of Formula Ia in formulations containing 3 mg/mL meta-cresol, 100 mg/mL SBE-CD and 10 mgA/mL compound of Formula Ia is shown in Table IX. Robust stability for both compound of Formula Ia and meta-cresol was demonstrated. The compound of Formula Ia experienced a 3% loss (relative to 1 week at 5° C.) after 12 weeks at 70° C., while the meta-cresol potency decreased by 2%.

TABLE IX

Stability of meta-cresol and compound of Formula Ia

Storage Condition	Timepoint	Compound of Formula Ia CONTENT (% INTENT) Amber-Treated	Compound of Formula Ia CONTENT (% INTENT) Amber-Untreated	meta-cresol CONTENT (% INTENT) Amber-Treated	meta-cresol CONTENT (% INTENT) Amber-Untreated
70° C.	1 week	94	94	100. . .	

DETD

A. A pharmaceutical composition comprising a therapeutically effective amount of an Active Pharmaceutical Ingredient, a .beta.-cyclodextrin, a pharmaceutically acceptable preservative, a pharmaceutically acceptable vehicle, and an optional pharmaceutically acceptable excipient, wherein the preservative demonstrates pharmaceutically acceptable antimicrobial preservative effectiveness.

B. The pharmaceutical composition according to preferred embodiment A wherein the .beta.-cyclodextrin is 2-hydroxypropyl-.beta.-cyclodextrin or sulfobutyl ether-.beta.-cyclodextrin.

C. The pharmaceutical composition according to preferred embodiment B wherein the preservative is selected from thimerosal, propylene glycol, phenol, or meta-cresol or a combination thereof.

D. The pharmaceutical composition according to preferred embodiments B or C wherein the preservative has a binding value to the cyclodextrin that is less than a binding value of the Active Pharmaceutical Ingredient to cyclodextrin.

E. The pharmaceutical composition according to preferred embodiment D, wherein the concentration of preservative is about 0.1 mg/mL to about 600 mg/mL.

F. The pharmaceutical composition according to preferred embodiment E, wherein the preservative is meta-cresol and the concentration of preservative is about 0.1 mg/mL to about 20 mg/mL.

G. The pharmaceutical composition according to preferred embodiment F wherein about 1 mg/mL to about 5 mg/mL of the meta-cresol is unsequestered in the cyclodextrin.

H. The pharmaceutical composition according to preferred embodiment G wherein about 2.5 mg/mL of the preservative is unsequestered in the cyclodextrin.

I. The pharmaceutical composition according to preferred embodiment D wherein the binding value of the Active Pharmaceutical Ingredient to cyclodextrin is between 500 M.sup.-1 and 10,000 M.sup.-1.

J. The pharmaceutical composition according to preferred embodiment I wherein the binding value of the Active Pharmaceutical Ingredient to cyclodextrin is between 800 M.sup.-1 and 3,000 M.sup.-1.

K. The pharmaceutical composition according to preferred embodiment D wherein the Active Pharmaceutical Ingredient has a greater than or equal to two-fold binding constant with cyclodextrin over that of the preservative.

L. The pharmaceutical composition according to preferred embodiment K wherein the binding constant is greater than or equal to. . . I, ##STR9## wherein R.sup.2 is selected from the group consisting of methyl, ethyl, isopropyl, sec-butyl and tertbutyl, a pharmaceutically acceptable .beta.-cyclodextrin, a pharmaceutically acceptable preservative, a pharmaceutically acceptable vehicle and an optional pharmaceutically acceptable excipient.

U. The pharmaceutical composition according to preferred embodiment T wherein the .beta.-cyclodextrin is 2-hydroxypropyl-.beta.-cyclodextrin or sulfobutyl ether-.sym.-cyclodextrin.

V. The pharmaceutical composition according to preferred embodiment U wherein the pharmaceutically acceptable preservative is selected from thimerosal, propylene glycol, phenol or meta-cresol, or a combination thereof.

W. The pharmaceutical composition according to preferred embodiment V wherein the preservative is meta-cresol.

X. The pharmaceutical composition according to preferred embodiment W having a pH in a range of about 4 to. . . The pharmaceutical composition according to preferred embodiments W or X wherein about 1 mg/mL to about 5 mg/mL of the preservative is unsequestered in the cyclodextrin.

Z. The pharmaceutical composition according to preferred embodiment Y wherein the compound of Formula I, or a pharmaceutically acceptable salt thereof, is in an amount of about 0.1 mg/mL to about 100 mg/mL and the .beta.-cyclodextrin is in an amount of about 20 mg/mL to about 200 mg/mL and the preservative is meta-cresol.

A1. A pharmaceutical composition according to preferred embodiment Z wherein the .beta.-cyclodextrin is in the amount of 55 mg/mL to 100 mg/mL and the meta-cresol is an amount of about 2.5 mg/mL to 3.5 mg/mL.

B1. A pharmaceutical composition according to preferred embodiments T,. . . or a pharmaceutically acceptable salt thereof, is in an amount of about 0.1 mg/mL to about 100 mg/mL and the .beta.-cyclodextrin is in an amount of about 20 mg/mL to about 200 mg/mL and the preservative is meta-cresol and is in an amount of about 1 mg/mL to about 5 mg/mL.

D1. The pharmaceutical composition according to preferred embodiment C1 wherein the .beta.-cyclodextrin is in an amount of about 55 mg/mL to about 100 mg/mL and the preservative is meta-cresol and is in an amount of about 2.5 mg/mL to about 3.5 mg/mL.

E1. The pharmaceutical composition according to preferred embodiment D1

wherein the .beta.-cyclodextrin is sulfobutyl ether-.beta.-cyclodextrin .

F1. A pharmaceutical composition comprising the compound of Formula Ia, ##STR11## or its pharmaceutically acceptable salts, wherein the compound of Formula Ia is 10 mgA/mL, sulfobutyl ether -.beta.-cyclodextrin is in an amount of about 63 mg/mL and meta-cresol is in an amount of about 3.3 mg/mL, a pharmaceutically acceptable vehicle and an optional pharmaceutically acceptable excipient.

G1.. . . an aqueous pharmaceutical composition comprising the pharmaceutical composition of preferred embodiments T, U, V, W, X, F1 or G1, the .beta.-cyclodextrin being present in amounts which are sufficient for improved injection toleration at the injection site.

I1. A method for. . . is citrate.

O1. A method to develop preserved API compositions comprising a therapeutically effective amount of an API, a .beta.-cyclodextrin and a pharmaceutically acceptable preservative.

P1. The method according to preferred embodiment O1 wherein the preservative has a binding value to the cyclodextrin that is less than a binding value of the API to cyclodextrin.

Q1. The method according to preferred embodiment P1 wherein the preservative is selected from thimerosal, glycol, phenol or meta-cresol or a combination thereof

R1. The method of preferred embodiments P1 or Q1 wherein the binding value of the API with the cyclodextrin is greater than 50 M.sup.-1.

S1. The method of preferred embodiment R1 wherein the binding value of the API with the cyclodextrin is between 500 and 10,000 M.sup.-1.

T1. The method of preferred embodiment S1 wherein the binding value of the API with the cyclodextrin is between 800 and 3,000 M.sup.-.

U1. The method of preferred embodiment T1 wherein Antimicrobial Effectiveness Test (AET) requirements. . .

CLM What is claimed is:
11. A pharmaceutical composition comprising a therapeutically effective amount of an Active Pharmaceutical Ingredient, a .beta.-cyclodextrin, a pharmaceutically acceptable preservative , a pharmaceutically acceptable vehicle, and an optional pharmaceutically acceptable excipient, wherein said preservative demonstrates pharmaceutically acceptable antimicrobial preservative effectiveness.

CLM What is claimed is:
13. The pharmaceutical composition according to claim 12 wherein the .beta.-cyclodextrin is 2-hydroxypropyl-.beta.-cyclodextrin or sulfobutyl ether-.beta.-cyclodextrin .

CLM What is claimed is:
14. The pharmaceutical composition according to claim 12 wherein the preservative is selected from thimerosal, propylene glycol, phenol, or meta-cresol or a combination thereof.

CLM What is claimed is:
15. The pharmaceutical composition according to claim 14 wherein the preservative is about 2.5 mg/ml of meta-cresol .

CLM What is claimed is:
16. The pharmaceutical composition according to claim 14 wherein the preservative has a binding value to the cyclodextrin that is less than a binding value of the Active Pharmaceutical Ingredient to cyclodextrin.

CLM What is claimed is:
17. The pharmaceutical composition according to claim 15 wherein about 1 mg/mL to about 5 mg/mL of the preservative is unsequestered in the cyclodextrin.

CLM What is claimed is:
18. The pharmaceutical composition according to claim 16 wherein the binding value of the Active Pharmaceutical Ingredient to cyclodextrin is between 500 M.sup.-1 and 10,000 M.sup.-1.

CLM What is claimed is:
19. The pharmaceutical composition according to claim 16 wherein the binding value of the Active Pharmaceutical Ingredient to cyclodextrin is between 800 M.sup.-1 and 31,000 M.sup.-1.

ST antimicrobial preservative cyclodextrin liq dosage form

IT Tachykinin antagonists
(NK1 receptor antagonists; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT Preservatives
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT Drug delivery systems
(liqs.; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT Drug delivery systems
(parenterals; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT 35963-20-3 85943-26-6 155681-48-4
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT 147116-67-4P
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT 359875-09-5P 863879-46-3P
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT 54-64-8, Thimerosal 57-55-6, Propylene glycol, biological studies 108-39-4, m-Cresol, biological studies 108-95-2, Phenol, biological studies 7585-39-9, β -Cyclodextrin 7585-39-9D, β -Cyclodextrin, ethers 147116-68-5 863879-43-0 863879-44-1 863879-45-2
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

INCL INCLM: 514/058.000
INCLS: 514/305.000

NCL NCLM: 514/058.000
NCLS: 514/305.000

IC IPCI A61K0031-724 [I,A]; A61K0031-716 [I,C*]
IPCR A61K0031-716 [I,C]; A61K0031-724 [I,A]

CHEMICAL ABSTRACTS INDEXING COPYRIGHT 2009 ACS on STN

	PATENT	KIND	DATE
OS	CA 143:272554 * WO 2005082416	A2	20050909

* CA Indexing for this record included

CC 63-6 (Pharmaceuticals)

ST antimicrobial preservative cyclodextrin liq dosage form

IT Tachykinin antagonists
(NK1 receptor antagonists; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT Preservatives
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT Drug delivery systems
(liqs.; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT Drug delivery systems
(parenterals; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT 35963-20-3 85943-26-6 155681-48-4
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT 147116-67-4P
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT 359875-09-5P 863879-46-3P
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT 54-64-8, Thimerosal 57-55-6, Propylene glycol, biological studies 108-39-4, m-Cresol, biological studies 108-95-2, Phenol, biological studies 7585-39-9, β -Cyclodextrin 7585-39-9D, β -Cyclodextrin, ethers 147116-68-5 863879-43-0 863879-44-1 863879-45-2
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

L20 ANSWER 4 OF 6 USPATFULL on STN

ACCESSION NUMBER:	2007:148231 USPATFULL		
TITLE:	Pharmaceutical compositions of neurokinin receptor antagonists and cyclodextrin and methods for improved injection site toleration		
INVENTOR(S):	Boettner, Wayne, Noank, CT, UNITED STATES Miskell, Christine, Colchester, CT, UNITED STATES		

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 20070129328	A1	20070607	
APPLICATION INFO.:	US 2005-587808	A1	20050106	(10)
	WO 2005-IB20		20050106	
			20060728	PCT 371 date

	NUMBER	DATE
PRIORITY INFORMATION:	US 2004-540644P	20040130 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	PHARMACIA & UPJOHN, 7000 Portage Road, KZO-300-104,

KALAMAZOO, MI, 49001, US
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1-10
LINE COUNT: 1055
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Pharmaceutical compositions of neurokinin receptor antagonists and cyclodextrin and methods for improved injection site toleration

AB . . . compositions with an improved injection site toleration comprising an effective amount of a neurokinin receptor antagonist with a pharmaceutically acceptable cyclodextrin. The invention is also directed to pharmaceutical compositions of the compound of Formula (I), wherein R.sup.2 is selected from the. . . ethyl, isopropyl, sec-butyl and tert-butyl. The invention is also directed to pharmaceutical compositions of the compound of Formula Ia, and cyclodextrins and methods for improved injection site toleration thereof. ##STR1##

SUMM The present invention is directed to pharmaceutical compositions containing cyclodextrins for improved injection site toleration and neurokinin receptor (NK-1) antagonists. The invention is also directed to pharmaceutical compositions of the. . .

SUMM In particular, the invention is directed to pharmaceutical compositions of the compound of Formula Ia, (2S,3S)-2-benzhydryl-N-(5-tert-butyl-2-methoxybenzyl)quinuclidin-3-amine, and cyclodextrins for improved injection site toleration. ##STR3##

SUMM It was determined that improved injection site toleration was realized by the addition of a cyclodextrin to the pharmaceutical composition containing a neurokinin receptor antagonist. Cyclodextrins are cyclic oligosaccharides. There are three main cyclodextrins: α- cyclodextrin is composed of a ring of six glucose residues; .beta.-cyclodextrin is composed of a ring of seven glucose residues; and γ-cyclodextrin is composed of a ring of eight glucose residues. Typically, cyclodextrins are formed by the action of an amylase on starch. Cyclodextrins typically vary in shape and size, but are, generally, defined by the presence of a hydrophobic cavity and can form. . . with other organic molecules, with salts, and with halogens either in solid state or in aqueous solution. Methods for preparing cyclodextrins are well known to those of skill in the art and many cyclodextrins are commercially available.

SUMM Cyclodextrins have been utilized in attempts to improve injection site tolerance. For example, WO/0062793 to Vasudevan, et al. discloses methods and compositions for treating fungal infections that include formulations of a pseudomycin or related anti-fungal agent and a cyclodextrin. U.S. Pat. No. 6,048,845 to Rubinfeld discloses compositions of matter including a substituted cyclodextrin and cytotoxic compound. U.S. Pat. No. 5,024,998 to Bodor discloses aqueous parenteral solutions of drugs that are insoluble or only sparingly soluble in water and/or that are unstable in water, combined with hydroxypropyl-62 -cyclodextrin.

SUMM . . . amount of a neurokinin receptor (NK-1) antagonist, such as those described in the references cited herein, with a pharmaceutically acceptable cyclodextrin. Further neurokinin receptors are disclosed in U.S. Pat. No. 5,807,867, U.S. Pat. No. 6,222,038, U.S. Pat. No. 6,255,320, U.S. Pat.. . .

SUMM In one embodiment, the cyclodextrin is selected from a pharmaceutically acceptable .beta.-cyclodextrin, hydroxypropyl .beta.-cyclodextrin, sulfobutylether .beta.-cyclodextrin ("SBE-CD") or substituted cyclodextrins. In another embodiment, the cyclodextrin is about 2% to about 40% of the vehicle by weight. Preferentially, the

cyclodextrin is about 4% to about 20% of the composition. More preferably, the cyclodextrin is about 5% to about 10% of the composition and is hydroxypropyl .beta.-cyclodextrin or SBE-CD.

SUMM . . . an aqueous pharmaceutical solution comprising the pharmaceutical composition described above in a therapeutically effective amount sufficient for treating emesis, the cyclodextrin being present in amounts that are sufficient for improving injection toleration at the injection site.

SUMM The term "cyclodextrin" as used herein means a cyclic oligosaccharide having a hydrophobic interior cavity and a hydrophilic exterior. There are three main types of cyclodextrins: α- cyclodextrin, .beta.-cyclodextrin and γ- cyclodextrin. The term "cyclodextrin" also includes various substituted cyclodextrins, including as side chains any organic moiety or a heteroorganic moiety. Substituted cyclodextrins also include cyclodextrins that have been alkylated, hydroxyalkylated, or reacted to form a sulfoalkyl ether.

SUMM As used herein, cyclodextrins and/or substituted cyclodextrins include, but are not limited to, sulfobutylether cyclodextrin, hydroxypropyl cyclodextrin, hydroxyethyl cyclodextrin, glucosyl cyclodextrin, maltosyl cyclodextrin, hydroxypropyl-.beta.-cyclodextrin, sulfobutylether-.beta.-cyclodextrin, hydroxyethyl-.beta.-cyclodextrin, hydroxypropyl-γ- cyclodextrin, hydroxyethyl-.beta.-cyclodextrin, dihydroxypropyl-.beta.-cyclodextrin, glucosyl-.beta.-cyclodextrin, diglycosyl-.beta.-cyclodextrin, maltosyl-.beta.-cyclodextrin, maltosyl-γ-cyclodextrin, maltotrialsyl-.beta.-cyclodextrin, maltotrialsyl-γ- cyclodextrin, dimaltosyl-.beta.-cyclodextrin, cyclodextrin derivatives, various mixtures of cyclodextrin derivatives thereof, mixtures such as maltosyl-.beta.-cyclodextrin /dimaltosyl-.beta.-cyclodextrin, and any other similar cyclodextrin known to those of skill in the art.

SUMM . . . making the compositions of the invention (including but not limited to e.g. water for injection, water, water miscible organic solvents, propylene glycol, 2-pyrrolidone, ethanol, n-methyl pyrrolidone, polyethylene glycol, glycerol formal, oily vehicles, sesame oil, safflower oil and the like)

DETD . . . acceptable salt of the compound of Formula Ia may also be used, such as the citrate or malate salts. A cyclodextrin is added to the solution in a concentration range of about 2% to about 40%. Preferably, the cyclodextrin comprises about 4% to about 20% of the pharmaceutical composition and more preferably about 5% to about 10%. Preferably, the cyclodextrin is a .beta.-cyclodextrin: hydroxypropyl .beta.-cyclodextrin, sulfobutylether .beta.-cyclodextrin or other pharmaceutically acceptable substituted .beta.-cyclodextrin.

DETD The pharmaceutical compositions can further include a preservative to prevent microbial contamination, as more fully described in U.S. Provisional Application, contemporaneously filed, commonly owned and assigned to Pfizer, Inc. The above application is incorporated by reference in its entirety for all purposes. As used herein, the word "preservative" means a compound, or combination of compounds, added to prevent or inhibit the growth of microorganisms which could present a. . .

DETD Any of the compositions and/or pharmaceutical compositions described above can be administered solely with the neurokinin receptor antagonist and the cyclodextrin. However, it is possible for additional ingredients to be included within the composition or pharmaceutical composition. Further, various conventional carriers. . .

DETD For those Examples having sulfobutylether .beta.-cyclodextrin ("SBE-CD") as part of the pharmaceutical composition, the sodium salt of SBE-CD was utilized.

DETD . . . prepared by dispersing 2.76 grams of the citrate salt of compound of Formula Ia in 193.33 grams of a 30% propylene glycol ("PG") solution (90.01 grams of PG dispersed in sufficient water for injection (218.53 grams) to make 300 mL of solution).. . .

DETD . . . by dissolving 2.88 grams of the citrate salt of compound of Formula Ia in 203.99 grams of a 10% hydroxypropyl R-cyclodextrin ("HPB-CD") solution (30.97 grams of HPB-CD dissolved in sufficient water for injection (213.62 grams) to make 300 mL of solution).. . .

DETD . . . 4 4 0.6 0 0 0.8 2.9 0 0.1

Formal
20% SBE J 10 4 1 0.1 0 0 0 0 0 0
Cyclodextrin
20% SBE J 10 4 1 0 0 0 0 0 0 0
Cyclodextrin
1% Calcium K 10 1 1 0 0 0 0.8 1.6 0 0.1
Chloride
pH 5.0
1% Calcium K 10 3 1 0 0. . . 1 0.2 0 0 1.6 6.6 0 0.1
Chloride
pH 4.1
5% SBE P 10 1 1 1.0 0 0 0 0 0
Cyclodextrin
pH 4.5
5% SBE P 10 4 1 0.1 0 0 0 0 0
Cyclodextrin
pH 4.5
1% Calcium Q 10 1 1 0.3 0 0 0 0 0
Chloride/
5% SBE -CD
1% Calcium Q 10 4 1. . .

DETD . . . an improved injection site toleration comprising a therapeutically effective amount of a neurokinin receptor (NK-1) antagonist with a pharmaceutically acceptable cyclodextrin.

DETD . . . thereof, wherein R.sup.2 is selected from the group consisting of methyl, ethyl, isopropyl, sec-butyl and tert-butyl with a pharmaceutically acceptable cyclodextrin.

DETD 5. The pharmaceutical composition according to Preferred embodiments 1, 2, 3 or 4 wherein the cyclodextrin is selected from .beta.-cyclodextrin, hydroxypropyl .beta.-cyclodextrin, sulfobutylether .beta.-cyclodextrin or substituted cyclodextrins.

DETD 6. The pharmaceutical composition according to Preferred embodiment 5

wherein the cyclodextrin is about 2% to about 40% of the composition.

DETD 7. The pharmaceutical composition according to Preferred embodiment 6 wherein the cyclodextrin is about 4% to about 20% of the composition.

DETD 8. A pharmaceutical composition according to Preferred embodiment 7 wherein the cyclodextrin is about 5% to about 10% of the composition.

DETD 9. A pharmaceutical composition according to Preferred embodiment 8 wherein the cyclodextrin is sulfobutylether .beta.-cyclodextrin or hydroxypropyl .beta.-cyclodextrin.

DETD . . . composition according to Preferred embodiment 5 in a therapeutically effective amount sufficient for treating emesis or improving anesthesia recovery, the cyclodextrin being present in amounts that are sufficient for improving injection toleration at the injection site.

DETD 14. The method according to Preferred embodiment 13 wherein the cyclodextrin is about 2% to about 40% of the composition.

DETD 15. The method according to Preferred embodiment 14 wherein the cyclodextrin is about 4% to about 20% of the composition.

DETD 16. The method according to Preferred embodiment 15 wherein the cyclodextrin is about 5% to about 10% of the composition.

DETD 17. The method according to Preferred embodiment 16 wherein the cyclodextrin is sulfobutylether .beta.-cyclodextrin or hydroxypropyl .beta.-cyclodextrin.

DETD 22. The method according to Preferred embodiment 21 wherein the cyclodextrin is about 2% to about 40% of the composition.

DETD 23. The method according to Preferred embodiment 22 wherein the cyclodextrin is about 4% to about 20% of the composition.

DETD 24. The method according to Preferred embodiment 23 wherein the cyclodextrin is about 5% to about 10% of the composition.

DETD 25. The method according to Preferred embodiment 24 wherein the cyclodextrin is sulfobutylether .beta.-cyclodextrin or hydroxypropyl .beta.-cyclodextrin.

CLM What is claimed is:

. . . an improved injection site toleration comprising a therapeutically effective amount of a neurokinin receptor (NK-1) antagonist with a pharmaceutically acceptable cyclodextrin.

CLM What is claimed is:

19. The pharmaceutical composition according to claim 12 wherein said cyclodextrin is selected from .beta.-cyclodextrin, sulfobutylether cyclodextrin, hydroxypropyl cyclodextrin, hydroxyethyl cyclodextrin, glucosyl cyclodextrin, maltosyl cyclodextrin, hydroxypropyl-.beta.-cyclodextrin, sulfobutylether-.beta.-cyclodextrin, hydroxyethyl-.beta.-cyclodextrin, hydroxypropyl-γ- cyclodextrin, hydroxyethyl-.beta.-cyclodextrin, dihydroxypropyl-.beta.-cyclodextrin, glucosyl-.beta.-cyclodextrin, diglycosyl-.beta.-cyclodextrin, maltosyl-.beta.-cyclodextrin, maltosyl-γ-cyclodextrin, maltotrialsyl-.beta.-cyclodextrin, maltotrialsyl-γ- cyclodextrin, dimaltosyl-.beta.-cyclodextrin, cyclodextrin derivatives, various mixtures of cyclodextrin derivatives thereof, mixtures such as maltosyl-.beta.-cyclodextrin

/dimaltosyl-.beta.-cyclodextrin, and any other similar cyclodextrin known to those of skill in the art.

CLM What is claimed is:
20. The pharmaceutical composition according to claim 19 wherein the cyclodextrin is selected from .beta.-cyclodextrin, hydroxypropyl .beta.-cyclodextrin, sulfobutylether .beta.-cyclodextrin or substituted cyclodextrins.

CLM What is claimed is:
21. The pharmaceutical composition according to claim 20 wherein the cyclodextrin is about 2% to about 40% of the composition.

CLM What is claimed is:
22. The pharmaceutical composition according to claim 21 wherein the cyclodextrin is about 4% to about 20% of the composition.

CLM What is claimed is:
23. The pharmaceutical composition according to claim 22 wherein the cyclodextrin is about 5% to about 10% of the composition.

CLM What is claimed is:
25. The pharmaceutical composition of (2S,3S)-2-benzhydryl-N-(5-tert-butyl-2-methoxybenzyl)quinuclidin-3-amine and a pharmaceutically acceptable cyclodextrin where said cyclodextrin is selected from the group consisting of .beta.-cyclodextrin, hydroxypropyl .beta.-cyclodextrin, sulfobutylether .beta.-cyclodextrin or substituted cyclodextrins.

ST neurokinin receptor antagonist cyclodextrin pharmaceutical

IT Tachykinin antagonists
(NK1 receptor antagonists; pharmaceutical compns. of neurokinin receptor antagonists and cyclodextrin)

IT Drug delivery systems
(injections; pharmaceutical compns. of neurokinin receptor antagonists and cyclodextrin)

IT Human
(pharmaceutical compns. of neurokinin receptor antagonists and cyclodextrin)

IT 7585-39-9, β -Cyclodextrin 7585-39-9D, β -Cyclodextrin, ethers 147116-67-4 147116-68-5 863879-43-0 863879-44-1 863879-45-2 863879-46-3 863984-38-7
(pharmaceutical compns. of neurokinin receptor antagonists and cyclodextrin)

INCL INCLM: 514/058.000
INCLS: 514/305.000

NCL NCLM: 514/058.000
NCLS: 514/305.000

IC IPCI A61K0031-724 [I,A]; A61K0031-716 [I,C*]; A61K0031-4745 [I,A]; A61K0031-4738 [I,C*]
IPCR A61K0031-716 [I,C]; A61K0031-724 [I,A]; A61K0031-4738 [I,C]; A61K0031-4745 [I,A]

CHEMICAL ABSTRACTS INDEXING COPYRIGHT 2009 ACS on STN

PATENT	KIND	DATE

OS CA 143:272556 * WO 2005082419 A1 20050909
* CA Indexing for this record included
CC 63-6 (Pharmaceuticals)
ST neurokinin receptor antagonist cyclodextrin pharmaceutical
IT Tachykinin antagonists
(NK1 receptor antagonists; pharmaceutical compns. of neurokinin receptor antagonists and cyclodextrin)
IT Drug delivery systems
(injections; pharmaceutical compns. of neurokinin receptor antagonists and cyclodextrin)
IT Human
(pharmaceutical compns. of neurokinin receptor antagonists and cyclodextrin)
IT 7585-39-9, β -Cyclodextrin 7585-39-9D, β -Cyclodextrin, ethers 147116-67-4 147116-68-5 863879-43-0 863879-44-1 863879-45-2 863879-46-3 863984-38-7
(pharmaceutical compns. of neurokinin receptor antagonists and cyclodextrin)

L20 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2005:984052 CAPLUS
DOCUMENT NUMBER: 143:272554
TITLE: Liquid dosage forms comprising antimicrobial preservatives and .beta.-cyclodextrins
INVENTOR(S): Adami, Roger Christopher; David, Frederick; Wood, Julia Ann
PATENT ASSIGNEE(S): Pfizer Products Inc., USA
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005082416	A2	20050909	WO 2005-IB100	20050117
WO 2005082416	A3	20060727		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005216709	A1	20050909	AU 2005-216709	20050117
AU 2005216709	B2	20080207		
CA 2554346	A1	20050909	CA 2005-2554346	20050117
EP 1713504	A2	20061025	EP 2005-702263	20050117
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, BA, HR, IS, YU				
BR 2005006496	A	20070213	BR 2005-6496	20050117
JP 2007519703	T	20070719	JP 2006-550330	20050117

CN 101090735	A	20071219	CN 2005-80003284		20050117
RU 2332997	C2	20080910	RU 2006-127422		20050117
IN 2006DN03736	A	20070420	IN 2006-DN3736		20060629
MX 2006PA08032	A	20060914	MX 2006-PA8032		20060713
KR 2006128973	A	20061214	KR 2006-715283		20060728
KR 834232	B1	20080530			
NO 2006003858	A	20061019	NO 2006-3858		20060829
US 20070155697	A1	20070705	US 2006-588070		20061213
PRIORITY APPLN. INFO.:			US 2004-540897P	P	20040130
			WO 2005-IB100	W	20050117

TI Liquid dosage forms comprising antimicrobial preservatives and .beta.-cyclodextrins

AB The present invention is directed to pharmaceutical compns. containing a therapeutically effective amount of an Active Pharmaceutical Ingredient (API), a cyclodextrin and a preservative. The invention is also directed to pharmaceutical compns. containing a NK1 antagonist (API) and a cyclodextrin and the preservative. Thus, a formulation containing m-cresol and the API was very stable.

ST antimicrobial preservative cyclodextrin liq dosage form

IT Tachykinin antagonists
(NK1 receptor antagonists; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT Preservatives
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT Drug delivery systems
(liqs.; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT Drug delivery systems
(parenterals; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT 35963-20-3 85943-26-6 155681-48-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT 147116-67-4P
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT 359875-09-5P 863879-46-3P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IT 54-64-8, Thimerosal 57-55-6, Propylene glycol, biological studies 108-39-4, m-Cresol, biological studies 108-95-2, Phenol, biological studies 7585-39-9, β -Cyclodextrin 7585-39-9D, β -Cyclodextrin, ethers 147116-68-5 863879-43-0 863879-44-1 863879-45-2
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)

IC ICM A61K047-00

CC 63-6 (Pharmaceuticals)

ST antimicrobial preservative cyclodextrin liq dosage

form
IT Tachykinin antagonists
(NK1 receptor antagonists; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT Preservatives
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT Drug delivery systems
(liqs.; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT Drug delivery systems
(parenterals; liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT 35963-20-3 85943-26-6 155681-48-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT 147116-67-4P
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT 359875-09-5P 863879-46-3P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
IT 54-64-8, Thimerosal 57-55-6, Propylene glycol, biological studies 108-39-4, m-Cresol, biological studies 108-95-2, Phenol, biological studies 7585-39-9, β -Cyclodextrin 7585-39-9D, β -Cyclodextrin, ethers 147116-68-5 863879-43-0 863879-44-1 863879-45-2
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(liquid dosage forms comprising antimicrobial preservatives and β -cyclodextrins)
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 6 OF 6 USPATFULL on STN
ACCESSION NUMBER: 2003:201456 USPATFULL
TITLE: Use of tachykinin antagonists, including NK-1 receptor antagonists, to modify unwanted behavior in dogs, cats and horses
INVENTOR(S): Bronk, Brian Scott, Gales Ferry, CT, UNITED STATES
Hickman, Mary Anne, East Lyme, CT, UNITED STATES
Kilroy, Carolyn Rose, Old Lyme, CT, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20030139443	A1	20030724
APPLICATION INFO.:	US 2002-199284	A1	20020719 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-306692P	20010720 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PFIZER INC, 150 EAST 42ND STREET, 5TH FLOOR - STOP 49,

NEW YORK, NY, 10017-5612
NUMBER OF CLAIMS: 33
EXEMPLARY CLAIM: 1
LINE COUNT: 1222
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.
SUMM . . . parenteral administration, solutions of a therapeutic compound of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if necessary and the liquid. . .
DETD . . . Placebo

Dosage form	Subcutaneous Injection	Dosage form	Subcutaneous
Injection			
Potency	69%	Potency	0%
Formulation	Dissolved in 20% (w/v) SBE SBE cyclodextrin in water to make a cyclodextrin in base equivalent solution in water of 5 mg/ml	Formulation	20% (w/v) water

IT 136870-97-8 136871-13-1 136871-15-3 136871-24-4 136871-25-5
136871-26-6 136871-27-7 136871-28-8 136871-30-2 136871-31-3
136871-32-4 136871-33-5 136871-35-7 136871-60-8 136871-65-3
136871-74-4 136871-76-6 136871-77-7 136871-86-8 136871-91-5
136871-96-0 136871-99-3 136872-01-0 136872-03-2 136872-04-3
136872-16-7 136872-20-3 136872-23-6 136872-26-9 136872-31-6
136872-35-0 136872-38-3 136899-46-2 136899-74-6 136982-36-0
136982-39-3 136982-40-6 145741-90-8 145741-98-6 145741-99-7
145742-01-4 145742-06-9 145742-11-6 145742-15-0 145742-16-1
145742-21-8 145742-22-9 145742-23-0 145742-24-1 145742-28-5
145742-33-2 146604-05-9 146604-06-0 146604-07-1 146604-10-6
146604-11-7 146604-12-8 146604-13-9 146682-86-2 146682-87-3
146682-88-4 146725-78-2 146725-79-3 147116-64-1
147116-65-2 147116-66-3 147116-67-4
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161443-41-0 161443-42-1 161443-43-2 161443-44-3 164154-82-9
164154-84-1 164154-85-2 164154-86-3 164154-88-5 164154-89-6
164154-90-9 164456-76-2 164456-77-3 179463-88-8 189557-97-9
189558-03-0 189558-13-2 189558-35-8 189558-37-0 189558-48-3
189558-93-8 189559-06-6 190839-44-2 249296-46-6 494745-16-3
(NK-1 receptor antagonists to modify unwanted anxiety behavior in companion animals)
INCL INCLM: 514/305.000
INCLS: 514/317.000; 514/326.000
NCL NCLM: 514/305.000
NCLS: 514/317.000; 514/326.000
IC [7]
ICM A61K031-454
ICS A61K031-49; A61K031-445
IPCI A61K0031-454 [ICM,7]; A61K0031-4523 [ICM,7,C*]; A61K0031-49 [ICS,7]; A61K0031-445 [ICS,7]

IPCR A61K0031-00 [I,C*]; A61K0031-00 [I,A]; A61K0031-4418 [I,C*]; A61K0031-4418 [I,A]; A61K0031-445 [I,C*]; A61K0031-445 [I,A]; A61K0031-4523 [I,C*]; A61K0031-454 [I,A]; A61K0031-46 [I,C*]; A61K0031-46 [I,A]; A61K0031-49 [I,C*]; A61K0031-49 [I,A]

CHEMICAL ABSTRACTS INDEXING COPYRIGHT 2009 ACS on STN

	PATENT	KIND	DATE
OS CA 138:131154 *	WO 03009848	A1	20030206

* CA Indexing for this record included

CC 1-11 (Pharmacology)

ST companion animal anxiety behavior NK1 receptor antagonist; dog anxiety behavior NK1 receptor antagonist; cat anxiety behavior NK1 receptor antagonist; horse anxiety behavior NK1 receptor antagonist

IT Animal
Anxiety
Anxiolytics
Cat (Felis catus)
Dog (Canis familiaris)
Drug delivery systems
Drug screening
Horse (Equus caballus)
Hyperkinesia
Nervous system agents
(NK-1 receptor antagonists to modify unwanted anxiety behavior in companion animals)

IT Tachykinin receptors
(NK1 antagonists; NK-1 receptor antagonists to modify unwanted anxiety behavior in companion animals)

IT Digestive tract, disease
(abnormal elimination; NK-1 receptor antagonists to modify unwanted anxiety behavior in companion animals)

IT Appetite
(disorder, abnormal feeding and drinking; NK-1 receptor antagonists to modify unwanted anxiety behavior in companion animals)

IT Behavior
Sleep
(disorder; NK-1 receptor antagonists to modify unwanted anxiety behavior in companion animals)

IT Emotion
(fear; NK-1 receptor antagonists to modify unwanted anxiety behavior in companion animals)

IT Behavior
(grooming; NK-1 receptor antagonists to modify unwanted anxiety behavior in companion animals)

IT Mental disorder
(phobia; NK-1 receptor antagonists to modify unwanted anxiety behavior in companion animals)

IT Behavior
(social, socialization disorders; NK-1 receptor antagonists to modify unwanted anxiety behavior in companion animals)

IT Drugs
(veterinary; NK-1 receptor antagonists to modify unwanted anxiety behavior in companion animals)

IT Behavior
(vocalization, and destructive behavior; NK-1 receptor antagonists to modify unwanted anxiety behavior in companion animals)

IT 136870-97-8 136871-13-1 136871-15-3 136871-24-4 136871-25-5
136871-26-6 136871-27-7 136871-28-8 136871-30-2 136871-31-3

136871-32-4 136871-33-5 136871-35-7 136871-60-8 136871-65-3
136871-74-4 136871-76-6 136871-77-7 136871-86-8 136871-91-5
136871-96-0 136871-99-3 136872-01-0 136872-03-2 136872-04-3
136872-16-7 136872-20-3 136872-23-6 136872-26-9 136872-31-6
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164154-90-9 164456-76-2 164456-77-3 179463-88-8 189557-97-9
189558-03-0 189558-13-2 189558-35-8 189558-37-0 189558-48-3
189558-93-8 189559-06-6 190839-44-2 249296-46-6 494745-16-3
(NK-1 receptor antagonists to modify unwanted anxiety behavior in companion animals)